



Armed Forces College of Medicine
AFCM



Cholesterol Metabolism

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INTENDED LEARNING OBJECTIVES (ILOs)



➤ **By the end of this lecture, You will be able to:**

1. Illustrate the steps of cholesterol synthesis and degradation.
2. Interpret regulation of cholesterol synthesis.
3. Describe biochemical basis of statin drugs

Case Scenario:

- A 35 year old woman presents with chest pain radiating to her left arm. She is diagnosed with myocardial infarction and her serum cholesterol was 600 mg/dl. The family history was positive for high cholesterol level.
- She is prescribed with statin drugs as statin inhibits HMG-CoA reductase .



<https://www.stylecraze.com/articles/effective-home-remedies-to-treat-chest-pain/>



What is the normal level of cholesterol?

**What is the HMG-CoA reductase
?enzyme**



?What is the action of statin drugs

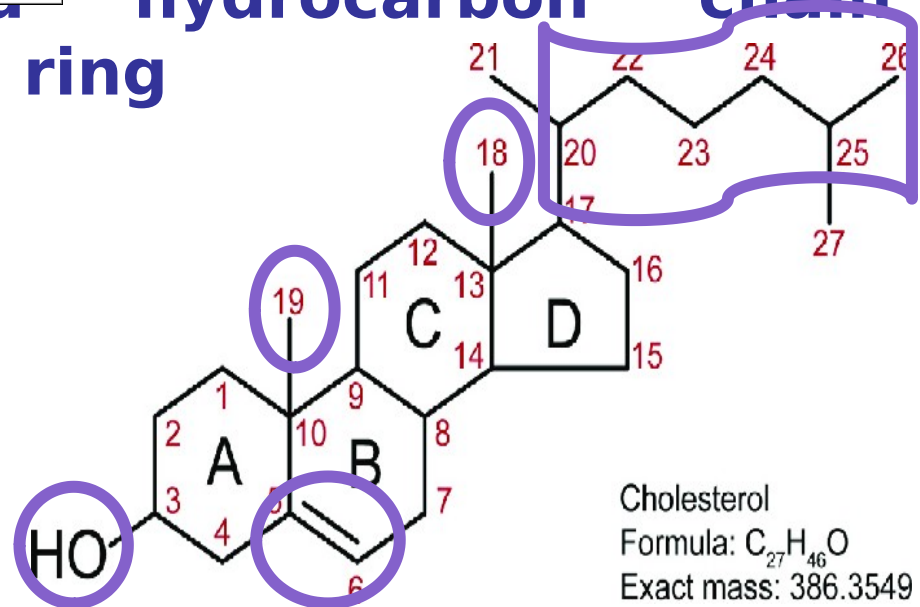
**How the body regulate cholesterol
? level**

Cholesterol Structure

Steroid numbering system

It consists of four fused hydrocarbon rings (A-D) called the “steroid nucleus,” with two CH₃ (C18&19) attached to C13&C10) and it has an eight-carbon, branched hydrocarbon chain attached to C17 of the D ring

Ring A has a hydroxyl group at C3, and ring B has a double bond between C5 and C6



Cholesterol
Formula: C₂₇H₄₆O
Exact mass: 386.3549

Cholesterol Esters

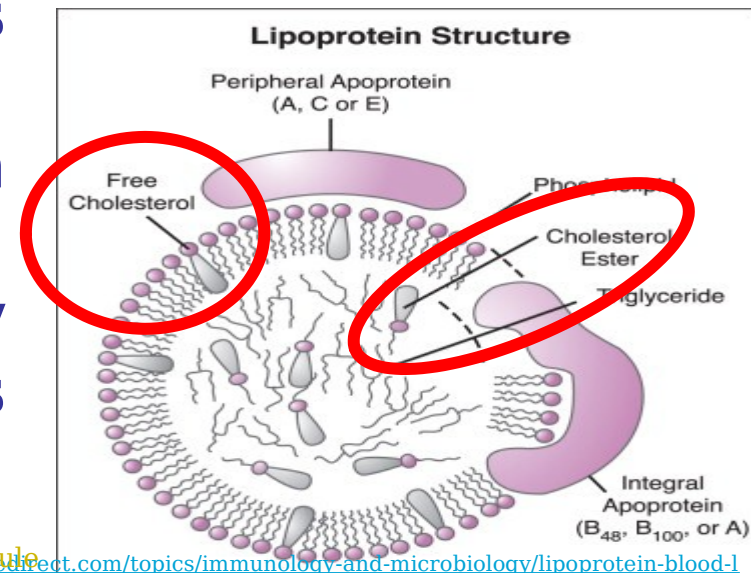
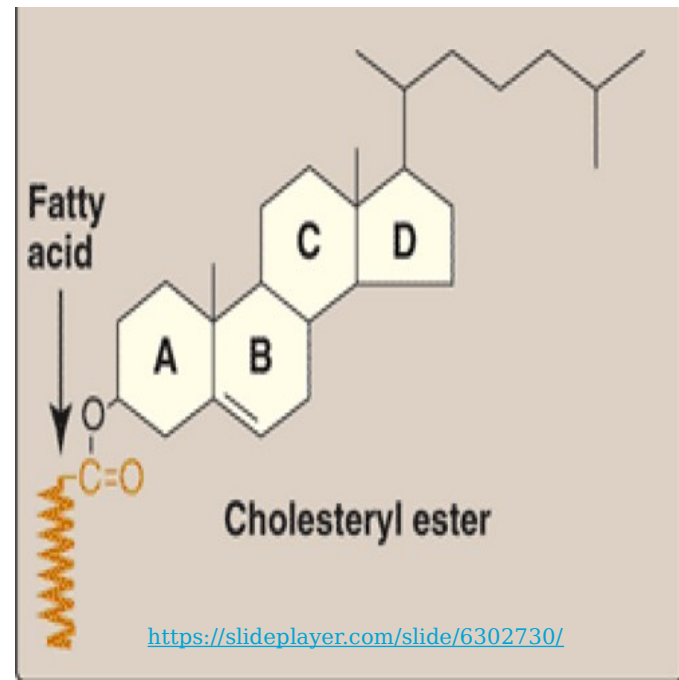
- Most plasma cholesterol is esterified with FA at C3 which is more hydrophobic than the free cholesterol.



- Because of hydrophobicity of Cholesterol and its Esters they are:

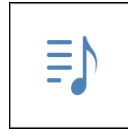
1- Transported as Lipoprotein particle OR

2- Solubilized by phospholipids and bile salts in the bile.



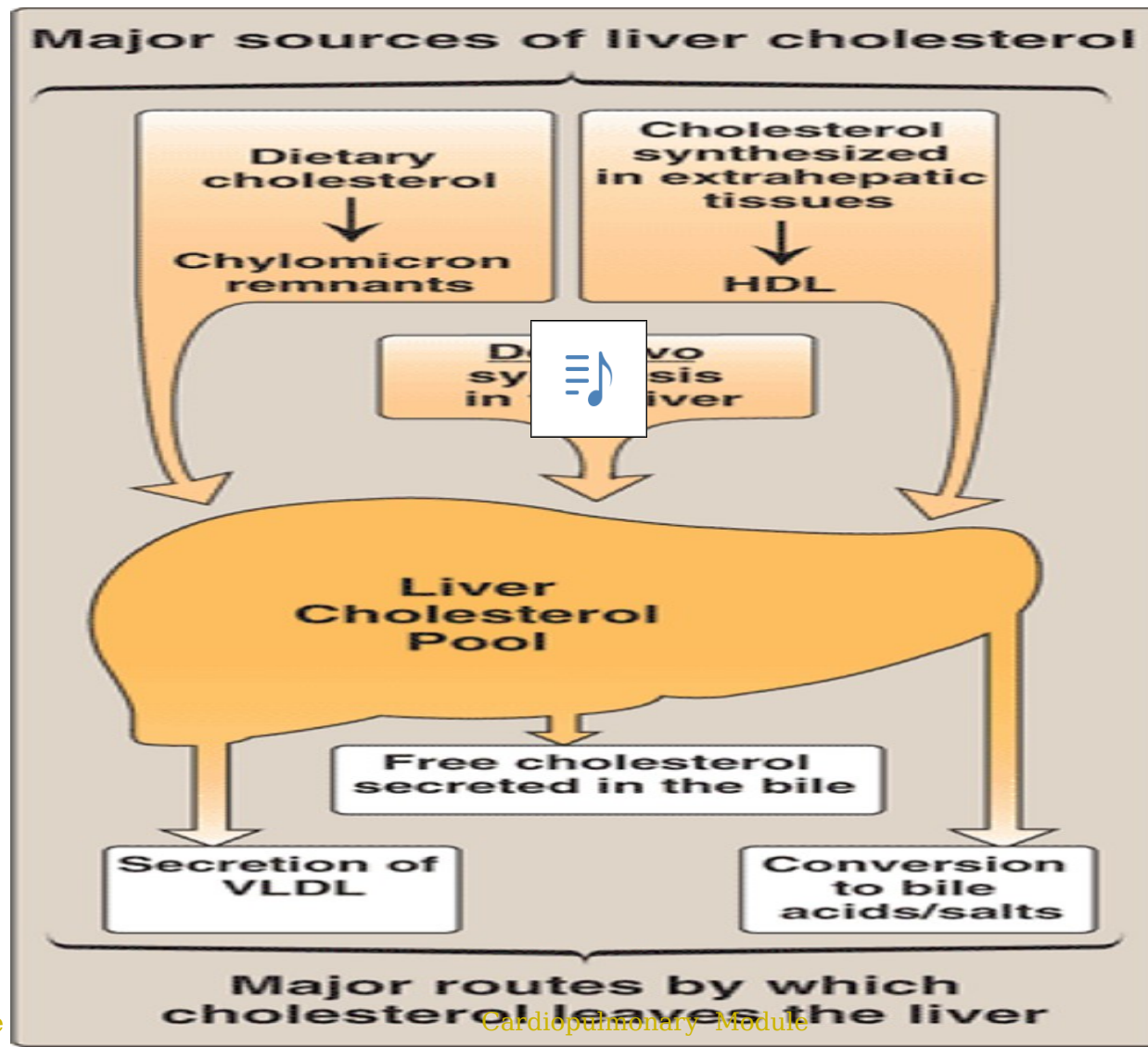
Functions of cholesterol:

1- As being a structural component of all cell membranes Modulating their fluidity



2- It is a precursor of bile acids, steroid hormones, and vit. D.

Role of liver in regulation of cholesterol:



<https://schoolbag.info/chemistry/biochemistry/18.html>

Synthesis of cholesterol:

- Cholesterol is synthesized by **virtually all tissues**.
- **All its carbons** are provided by **acetyl CoA** with help of **NADPH+H⁺**.
- Synthesis occurs in the  **cytoplasm**.

Synthesis
of HMG-
CoA

Synthesis
of
Mevalonate

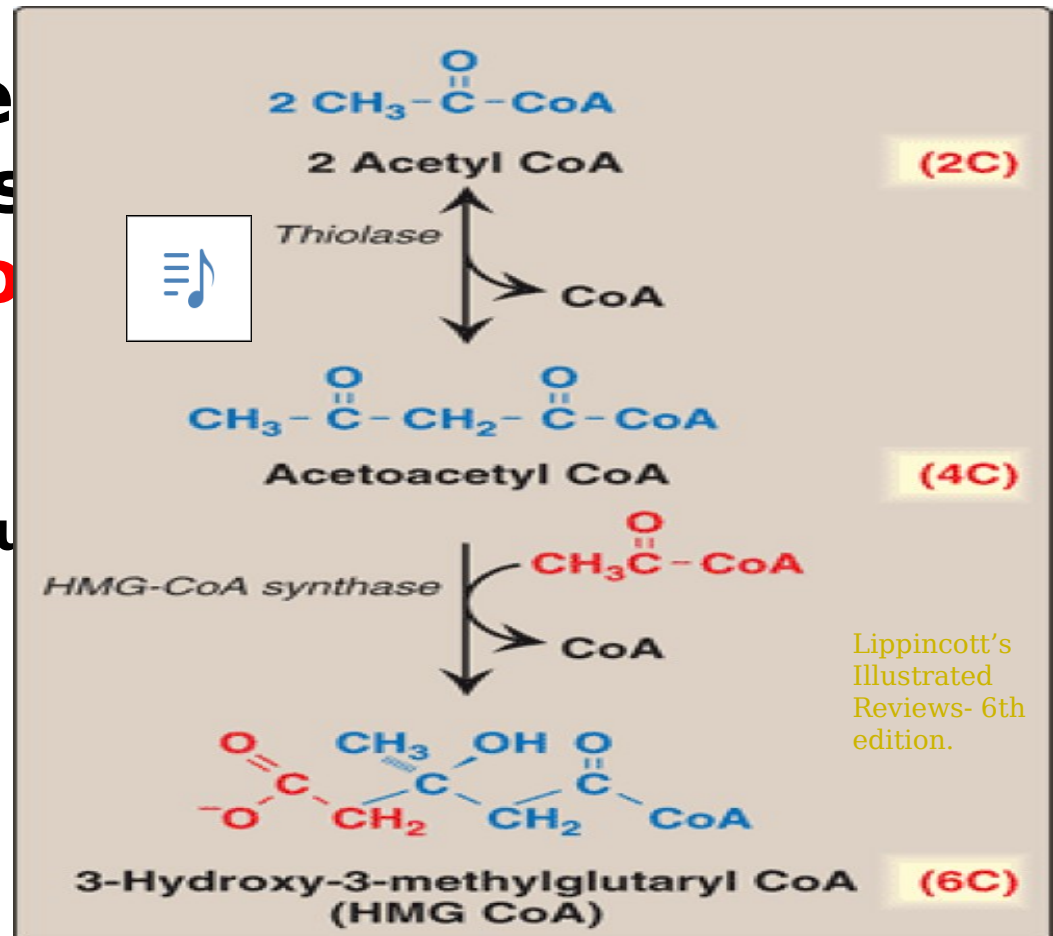
Mevalonate
into
Cholesterol

Synthesis of cholesterol:

1) Synthesis of HMG-CoA

- **1st 2 steps are in ketogenesis**
But with cytosolic Isoenzymes.

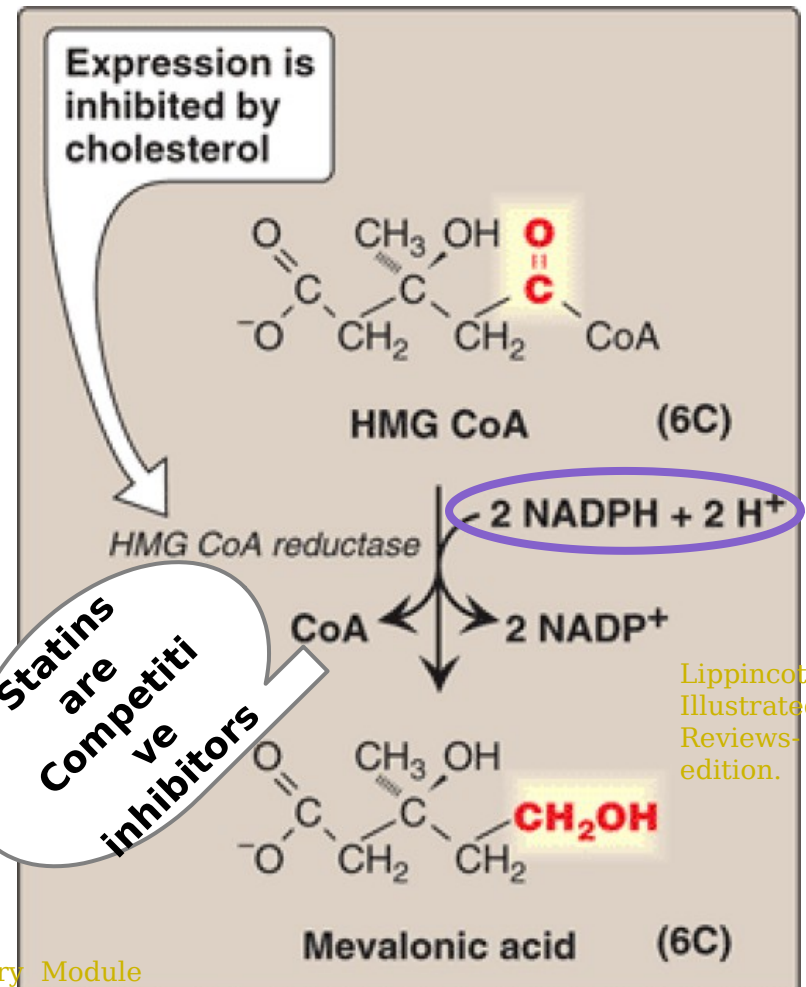
N.B. ketogenesis occurs in mitochondria



Synthesis of cholesterol:

2) Synthesis of Mevalonate

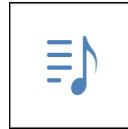
- Reduction occurs by **HMG CoA reductase**
- It is the **rate-limiting** key step in cholesterol synthesis.
- The reaction is **irreversible**.
- NB: this enzyme consumes 2 molecules of **NADPH+H**



Synthesis of cholesterol:

3) Mevalonate into Cholesterol

- Then, several steps occurs as follows:



**Mevalona
te (6C)**

**Isoperene
(5C)**

**Squalene
(30C)**

**Cholester
ol (27C)**

Excretion of cholesterol:

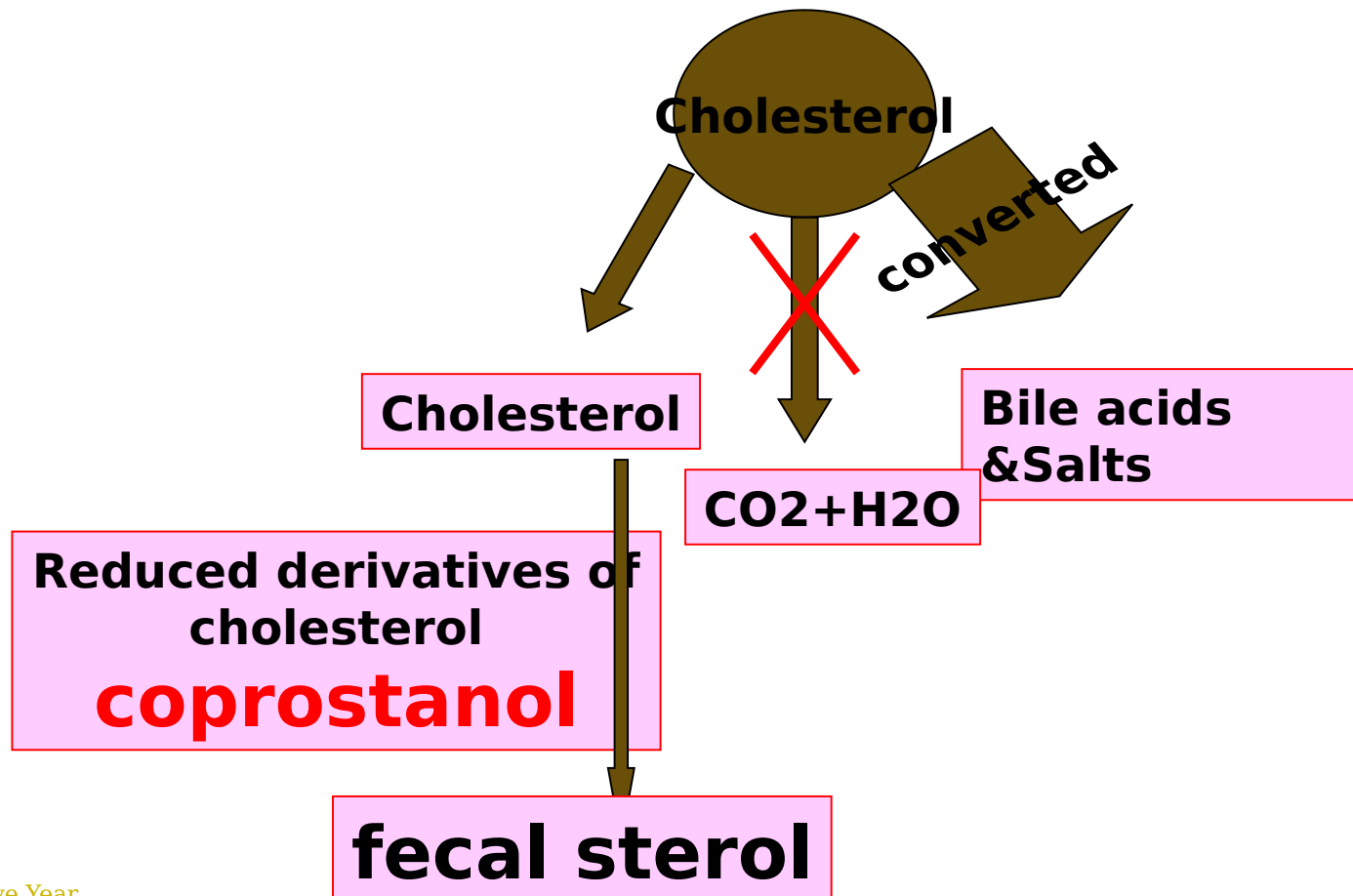
- The body **CAN NOT** be metabolized to CO_2 and H_2O

1- Cholesterol is converted  into bile, which transports it to the intestine.

2- Cholesterol also reaches the intestine reduced giving rise to **coprostanol**

(the major sterol in stools)

The ring structure of cholesterol cannot be metabolized to CO_2 and $???\text{H}_2\text{O}$. SO



Cholesterol can be degraded and gives high amount of energy

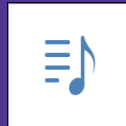
- **True**

- **False**



Regulation of cholesterol level:

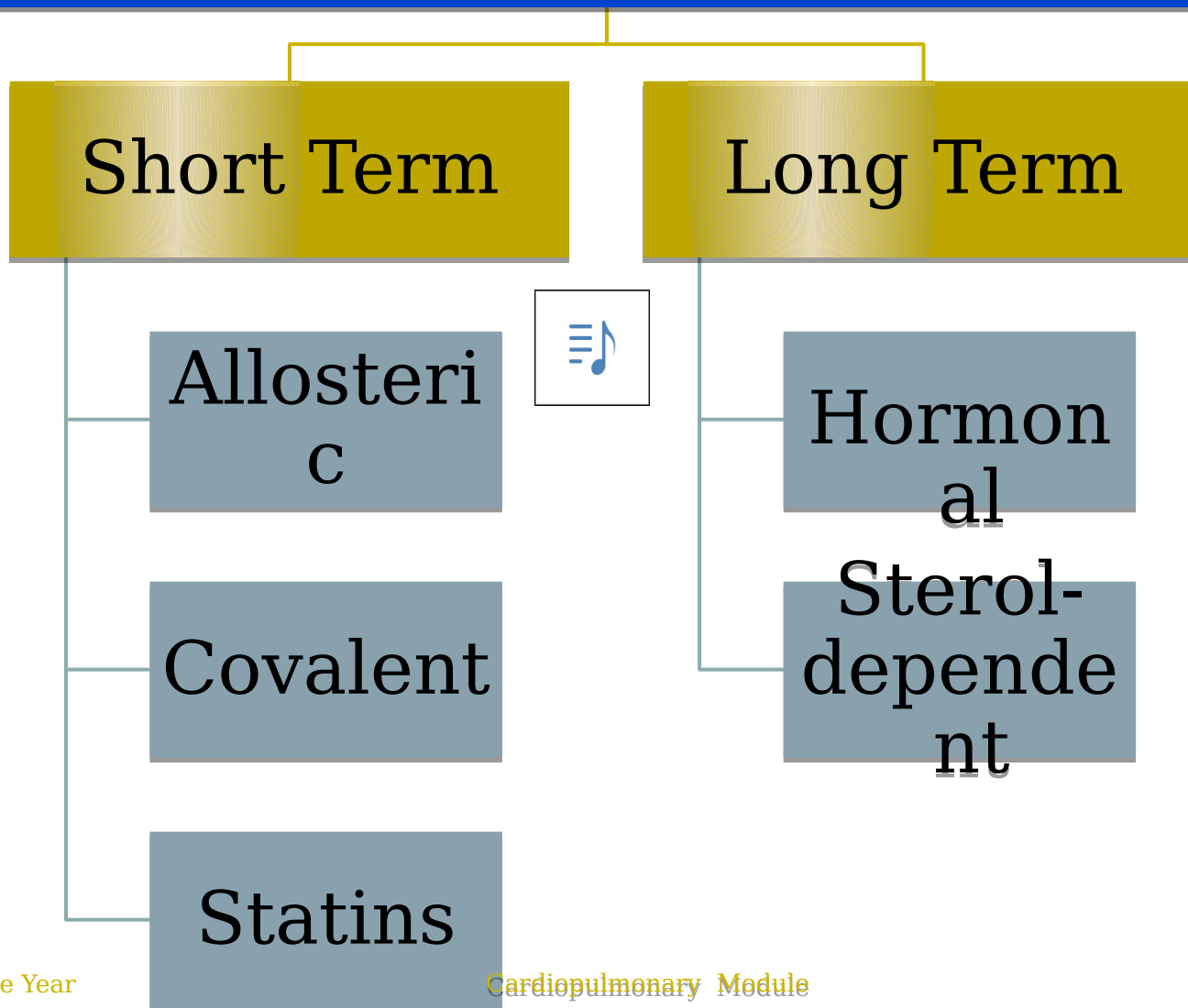
HMG-CoA reductase
(The committed/ The rate limiting step)



The normal blood level is (140-200 mg%).

<https://giphy.com/gifs/adhd-F0m17wsH0F0MBG>

Regulation of HMG- CoA reductase

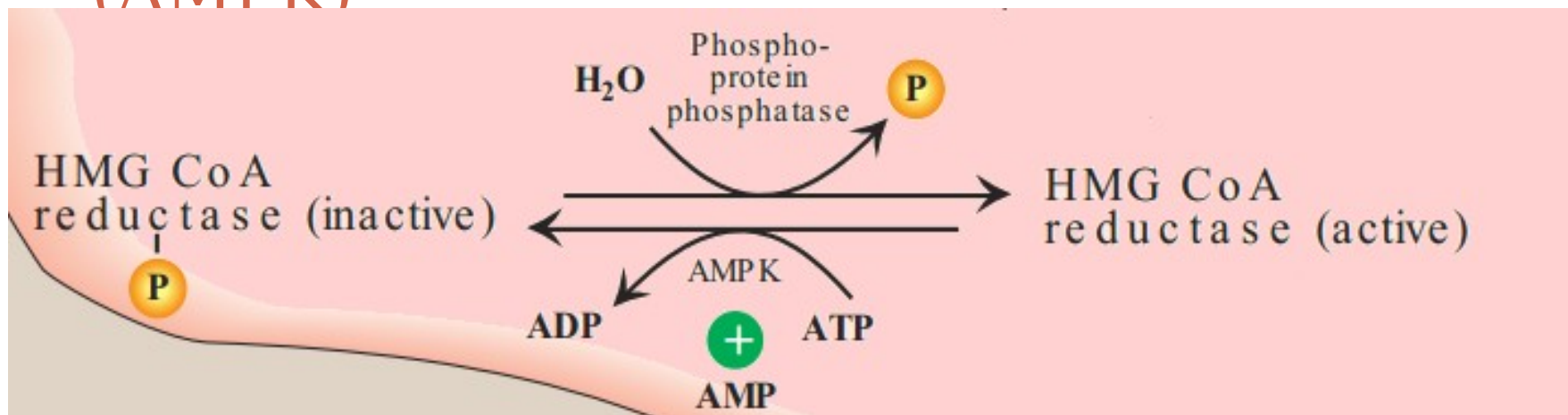


Allosteric Regulation :

Feedback inhibition by Mevalonate

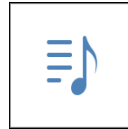
Covalent Modification:

- ↑ activity by Dephosphorylation
- ↓ activity by Phosphorylation through the action of AMP- activated protein kinase (AMPK)



Statins:

- Statin drugs (lovastatin, atrovastatin, and simvastatin) are **structural analogs of HMG CoA** acting as **reversible competitive inhibitors** of HMG CoA reductase.



- They are used in treatment of hypercholesterolemia



Hormonal long term regulation :

The amount of HMG CoA reductase itself is controlled hormonally.

Insulin, Thyroxin → Gene expression

Glucagon, glucocorticoids → ↓ Gene expression



Sterol- dependent long term regulation:

Low Cholesterol → ↑ Gene expression

High Cholesterol → ↓ Gene expression, ↑ proteolysis

The key regulatory enzyme of cholesterol synthesis is

- 1) Thiolase enzyme
- 2) HMG-CoA synthase enzyme
- 3) HMG-CoA reductase  enzyme
- 4) Cholesterol synthase
- 5) Mevalonate methylase

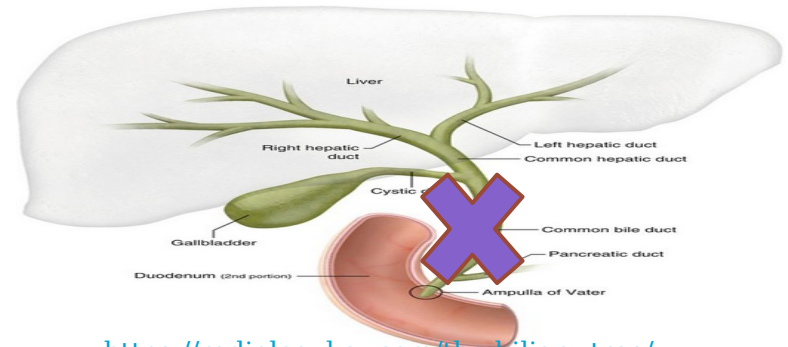


- **Hypercholesterolemia occurs in the following conditions:**

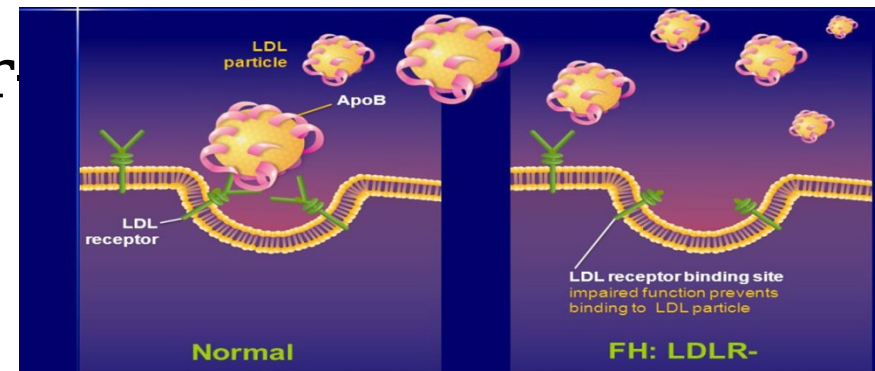
- 1- Hypothyroidism.
- 2- Diabetes mellitus.
- 3- Coffee drinking and cigarette smoking
- 4- Obstructive jaundice
- 5- Familial hypercholesterolemia.
- 6- Obesity (usually associated with hyperlipoproteinaemia).
- 7- Stress



<https://www.semanticscholar.org/paper/Thyroid-hormones%3A-a-potential-ally-to-agents-Duntas-Brenta/1918a95c45103ca306670e800c52f1afef3990ba/figure/0>



<https://radiologykey.com/the-biliary-tree/>



Key Points:

- **Cholesterol has many important functions.**
- **Cholesterol is synthesized by virtually all tissues.**
- **HMG CoA reductase is the rate limiting step for cholesterol synthesis.** 
- **Cholesterol can't be used as a source of energy.**
- **Statins are commonly used in treatment of hypercholesterolemia**
- **Diabetes, obesity and other medical problems may lead to hypercholesterolemia**

SUGGESTED TEXTBOOKS



- Lippincott's Illustrated Reviews- 6th edition.
- Harper's Illustrated Biochemistry-29th edition.



many
Thanks!